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★POLL/ B05 93-059347/08 ★CA 2070085-A

Combined time-release calcium chann l block r and ACE inhibitor - used for treating hypertension, congestive heart failure and other coronary diseases

- POLLI G P 91.05.31 91US-708425

C03 (92.12.01) A61K 31/40, 31/275

92.05.29 92CA-2070085

Compsn. comprises: (a) one or more calcium channel blocking agents; and (b) one or more ACE inhibitors; in time-release form in combination with a pharmaceutically effective carrier.

The Ca channel blocker is pref. diltiazlin, nicardipine, infedipine, nimodipene, verapemil, or a mixt. The ACE inhibitor is captopril, enalapril, lisinopril, trandolapril, or a mixt. Most pref. the combination is verapemil (V) and trandolapril (I), used in wt. ratio 90:1 in a core matrix.

USE/ADVANTAGE -The actions of (a) and (b) components complement each other in the disorders treatment, and are prescribed together, with (a) in time-release and (b) in immediate release formulation. For treatment of the disorders in long-term therapy, it is more effective, and convenient, to combine the two agents into a single compsn., so that ACE inhibitor levels are also maintained steady over at least 12-24 hr. period for the duration of the treatment. The compsn. is of esp. use to humans but can also be used for treatment of apes, monkeys, farm animals, dogs, and cats. Admin. is orally, once daily. (22pp Dwg.No.0/3)

C93-026534

5/9 WPIL - (C) Derwent Info. 1998
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XA - C93-026534
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DC - B05 C03
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(51) INTL.CL.[5] A61K-031/40; A61K-031/275

(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Ace Inhibitor and Calcium Channel Blocker for Use in Treating Hypertension

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(30) (US) 07/708,425 1991/05/31

(57) 10 Claims

Canada

ABSTRACT OF THE DISCLOSURE

A composition for the treatment f hypertension, congestive heart failure and other coronary problems in mammals, especially humans, has both a calcium channel blocker and an ACE inhibitor in time-released form in combination with a pharmaceutically acceptable vehicle. An improved method of treating hypertension involves administering a therapeutically effective amount of the aforesaid composition to a patient.

FIELD OF THE INVENTION

The present invention relates to a time-released pharmaceutical formulation of both a calcium channel blocking agent and an ACE inhibitor for the treatment of hypertension, congestive heart failure and related coronary ailments in mammals. The invention also relates to an improved method of treating the aforementioned coronary problems.

BACKGROUND OF THE INVENTION

Calcium channel blocking agents are very often the drug of choice in the treatment of angina pectoris, supraventricular tachycardia and hypertension. These agents are calcium-ion influx inhibitors (slow-channel blocking agents). Although their mechanism is not completely understood, they are thought to inhibit calcium ion entry through select voltage-sensitive intracellular calcium concentration in cardiac and vascular smooth muscle cells, they dilate coronary arteries and peripheral arteries and arterioles, and may reduce heart rate, decrease myocardial contractility (negative inotropic effect), and slow atrioventricular (AV) nodal conduction.

Typically, calcium channel blockers are incorporated into what is known in the pharmaceutical art as sustained release, sustained action, prolonged action, controlled release, extended action, timed release, depot and repository dosage forms. These identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single

dose. Thus, a timed-release formulation comprising a calcium channel blocker is made to release substantially all of the calcium antagonist over a period of time, usually over about 24 hours, rather than immediately as in a standard immediate-release formulation. Typically, then, a regimen of treatment with a calcium channel blocker would comprise administration of a single dose of a timed-release formulation once daily over a period extending up to several months or years.

Examples of calcium channel blockers include diltiazem, nicardipine, nifedipine, nimodipine and verapamil. These have been marketed under various tradenames. Formulations containing verapamil, for example, are described in U.S. Patent No.s 4,832,958, 4,863,742 and 4,927,565.

Angiotensin-converting enzyme (ACE) inhibitors have also been prescribed for the treatment of hypertension and congestive heart failure. The exact mechanism of antihypertensive action is unknown but may be related to competitive inhibition of angiotensin I-converting enzyme (ACE) activity, resulting in a decreased rate of conversion of angiotensin I to angiotensin II, which is a potent vasoconstrictor. Decreased angiotensin II concentrations result in a secondary increase in plasma renin activity (PRA), through removal of the negative feedback of renin release, and a direct reduction in aldosterone secretion.

Examples of ACE inhibitors include captopril, enalapril, lisinopril and trandolapril. Trandolapril, for example, is described in U.S. Patent No. 4,933,361.

Many times a calcium channel blocker is prescribed along with an ACE inhibitor. Formulations containing a combination of one ore more calcium channel blocking agents with one or more ACE inhibitors have also been formulated. The action of these drugs seems to complement one another in the treatment of hypertension and other coronary problems. These formulations are described, for example, in U.S. Patent No.s 4,931,430 and 4,808,413, as well as European Patent Application No. 0,311,382.

In instances where a calcium channel blocker and an ACE inhibitor have been utilized together in one composition or method of treatment, the calcium channel blocker has been formulated so as to be released over time, while the ACE inhibitor has been formulated to be released immediately to begin lowering ACE activity. (The term "immediate-release" as used herein means that the dissolution and absorption rates are not delayed by manipulation of the physical and/or chemical or other parameters of the drug itself or through modification of the drug release rate characteristics of the dosage that affect bioavailability). In fact, the prevailing wisdom has been that it is necessary not to delay the release of the ACE inhibitor. Moreover, there appears to have been a further reluctance to employ an ACE inhibitor in a time-released formulation because it has been felt that the quantity of the drug employed would have to be greatly increased in order to achieve a therapeutic response over time.

However, because hypertension and its related ailments are most typically chronic in nature, and because concomitant

therapy is also usually long-term, what is needed is a pharmaceutical composition and treatment regimen which will decrease ACE activity to a comparable level over a period of time, for example within about 12 to 24 hours after administration of the first dose, as compared with an immediate-release formulation. That is, there should be comparatively little or no difference in ACE activity levels when measured from a time period of within approximately 12 to about 24 hours, and beyond for the duration of the treatment.

Furthermore, what is needed is a method of treatment and composition utilizing both a calcium channel blocker and an ACE inhibitor in time-released form which will be at least as effective in treating hypertension in terms of decreasing ACE activity over a prolonged period, as measured by a time period starting from about 12 to 24 hours after beginning treatment, as are currently utilized treatment regimens which seek a marked reduction in ACE activity level immediately.

OBJECTS OF THE INVENTION

It is therefore an object of the present invention to provide a pharmaceutical composition comprising both a calcium channel blocking agent and an ACE inhibitor in time-released form for the treatment of hypertension and congestive heart failure in mammals, especially humans.

Another object of the invention is to provide a therapeutically effective quantity of a calcium channel blocker and

an ACE inhibitor in time-released form.

A further object of the invention is to provide a time-released formulation of a therapeutically effective quantity of verapamil and trandolapril.

Still another object of the present invention is to provide a time-released composition of both a calcium channel blocking agent and an ACE inhibitor which is as effective in the long-range treatment of high blood pressure and related coronary ailments as those compositions and regimens of treatment currently available in which the action of the ACE inhibitor is not delayed.

Another object of the invention is to provide an improved method of treating hypertension and coronary problems in which an effective quantity of a time-released formulation of a calcium channel blocker and an ACE inhibitor are administered on a periodic basis.

SUMMARY OF THE INVENTION

These and other objects of the invention are achieved by providing a pharmaceutical composition for the treatment of hypertension, congestive heart failure and other coronary ailments in mammals, e.g. humans, apes, monkeys, farm animals, dogs and cats, comprising a therapeutically effective quantity of both one or more calcium channel blocking agents and one or more ACE inhibitors in time-released form in combination with a pharmaceutically acceptable carrier.

Also provided as part of the invention is an improved

method of treating hypertension and related coronary problems in mammals which comprises administering to a patient a therapeutically effective quantity of a time-released formulation of one or more calcium channel blockers and one or more ACE inhibitors in combination with a pharmaceutically acceptable vehicle.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph of verapamil and norverapamil concentrations over time.

Figure 2 is a graph of trandolapril and trandolaprilat concentrations over time.

Figure 3 is a chart of ACE activity over time for the time-released formulation of verapamil and trandolapril according to a preferred embodiment of the invention versus ACE activity over time for an immediate release formulation of trandolapril.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In the composition according to the invention, one or more calcium channel blocking agents are employed together with one or more ACE inhibitors in a time-released formulation. The calcium antagonist may be any one selected from those known in the art and can include for example diltiazem, which has the chemical name 3-(acetyloxy)-5-[2-(dimethylamino)ethyl-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4-(5H)-one. Diltiazem is described in U.S. Patent No. 3,562,257. 4-Phenyl-1,4-

dihydropyridine calcium antagonists may also be employed, as well as nifedipine. Presently preferred is verapamil or 5-(3,4-dimethoxyphenylethyl)methyl-amino-2-(3,4-dimethoxyphenyl)-2-isopropyl valeronitrile, whose synthesis is described in U.S. Patent No. 3,261,859. Verapamil is marketed by Knoll Pharmaceuticals of Whippany, New Jersey under the tradename ISOPTIN - SR. Other calcium antagonists sold under various tradenames by other pharmaceutical companies are effective in the composition according to the invention, and are therefore also within the scope of the invention.

The calcium channel blocking agent is also preferably present in the form of a physiologically acceptable salt. Examples of these include the salts of such acids as hydrochloric acid, sulfuric acid, phosphoric acid, acetic acid, malonic acid, succinic acid, fumaric acid, maleic acid, citric acid, tartaric acid, lactic acid, ametosulfonic acid and oxalic acid. An especially desirable salt is hydrochloride. Thus, the most preferred calcium channel blocking agent for use in the time-released formulation according to the invention is verapamil HCl.

The ACE inhibitor which is employed in the composition according to the invention may also be selected from those currently available in the art. For example, these may include captopril, enalapril, ramipril, cilazapril and lisinopril, but presently preferred is trandolapril (N-1S-carbethoxy-3-phenylpropyl)-P-alanyl-2S, 3aR, 7aS-octahydroindol-2-carboxylic acid, from U.S. Patent No. 4,933,361). Other ACE inhibitors known

in the art and sold under various tradenames are also within the scope of the invention.

The ACE inhibitor may also be present in the form of a salt in the composition. Since trandolapril has both an acidic and a basic component, it can therefore form salts with both the aforementioned acids, as well as with physiologically compatible bases, such as alkali hydroxides of alkaline earth hydroxides.

The novel time-released composition of a calcium channel blocker and an ACE inhibitor may be processed with a pharmaceutically acceptable vehicle and can include one or more adjuvants, binders, fillers, preservatives, lubricants, tablet disintegrating agents, flow or viscosity regulators, softeners, wetting agents, dispersing agents, delaying agents and oxidizing agents. Examples of viscosity regulators include microcrystalline cellulose, sodium alginate and polyvinylpyrollidone. An example of a suitable lubricant would be magnesium stearate.

The calcium channel blocking agent(s), ACE inhibitor(s) and other ingredients are combined into a timed-release formulation. While parenteral as well as other routes of administration may be contemplated by those skilled in the art, it is preferred that oral dosage formulations be utilized.

Generally, there are two types of timed-release dosage form designs for oral administration.

One type involves the modification of the physical and/or chemical properties of the particular drugs utilized. The other involves the modification of the drug release rate characteristics

of the dosage form that affect bioavailability. Those skilled in the art may find it useful to conceive ways to alter the physical and/or chemical properties of the calcium channel clocking agent(s) and the ACE inhibitor(s) to achieve scope of the invention. It is preferred, however, that the approach to sustained release of both the calcium antagonist and the ACE inhibitor be based on dosage form modification.

Formulations based on modification of the physicochemical properties of the dosage forms can generally be classed into four basic product types: encapsulated slow release beads (or granules), tabletted slow release granulations, slow release core tablets ("matrix" for example), and osmotic release tablets. Numerous variations of these product typed exist in the art, and the particular one chosen will often depend on the specific drug properties such as solubility, dissociation constant, and stability, as well as on the manufacturing technology available.

The composition according to the invention may be incorporated into any one of the aforementioned dosage forms, and may even be incorporated under a liquid dosage form. It is preferred, however, that the composition according to the invention be incorporated into a slow release core tablet comprising a core matrix of both calcium channel blocker and ACE inhibitors. In this way, the manufacture of the tablets allows for the direct incorporation of loading doses, by preparation of either multilayered or press-coated tablets. One layer of the outer coat of the tablet is prepared from a potentially rapid disintegrating

granulation, leaving the less quickly disintegrating layer or core, which contains the maintenance dose.

The particular time-release oral formulation utilized should permit dissolution and absorption of the ACE inhibitor so that the ACE activity will approximate that of a standard immediate-release formulation after a set period of time, for example after about 12 to 24 hours is preferred. Those skilled in the art may contemplate somewhat longer or shorter periods.

Thus, while the widely accepted immediate-release formulation will generally have a more marked effect on ACE activity after approximately 1 to 4 hours, in a longer time frame as set forth above, and especially after several days or even weeks or months of treatment, the ACE activity level for the two formulations should be approximately the same.

Another advantage of the composition according to the invention lies in its relative ease and simplicity of manufacture. Both the ACE inhibitor and calcium channel blocker are directly mixed together into the slow-release matrix, which helps to eliminate the chance of developing defective lots.

In a particularly preferred embodiment of the invention the timed-release composition will comprise the calcium channel blocker verapamil HCl and the ACE inhibitor trandolapril in about a 90 to 1 weight ratio. A particularly suitable dosage form will comprise about 180 mg of verapamil HCl with about 2 mg of trandolapril in combination with a pharmaceutically acceptable vehicle to be orally administered once daily. The total weight of

a single dosage form will be approximately 540 to 545 mg., with binders and viscosity agents etc. comprising the remainder of the dosage form. This preferred dosage form will be in the form of a slow release core tablet comprising a core matrix of verapamil and trandolapril.

Those skilled in the art may find other weight ratios of calcium channel blocker to ACE inhibitors to be effective in a regimen of treatment consistent with the goal of maintaining the ACE activity level at a certain therapeutic level for the duration of extended or long-range treatment. Factors to be considered may include, for example, the level of treatment and results desired, as well as the weight, age and conditions of the patient and his or her tolerance ability. Thus, actual ratios may of course vary outside the preferred range set forth herein.

The following examples illustrate the invention, and should in no way be construed as limiting the scope thereof:

EXAMPLE 1

This example illustrates a method of preparing an especially preferred embodiment according to the invention, wherein especially preferred binders and viscosity agents etc. and their quantities are set forth.

1.800 kg of verapamil HCl, 20 g of trandolapril, 2.400 kg of sodium alginate, 0.541 kg of microcrystalline cellulose and 0.360 kg of polyvinylpyrollidone were mixed in a small P-K blender

for approximately 35 minutes. The resulting mixture was then transferred to a H bart mixer and 1.350 kg f purified water was added and mixed for about 10 minutes. 150 g of alcohol (9.5%) was then added and the resulting mixture blended for another 5 minutes. The yield was approximately 10,000 tablets of about 542 mg. each.

Dissolution rates of the aforementioned preferred dosage form showed that the trandolapril is released as follows: about 13% after approx. 1 hour, about 20% after approx, 2 hours, about 41% after approx. 3.5 hours, about 63% after approx. 5 hours, and 95% after approx. 8 hours. These results are based on the average dissolution/release rates for six samples of tablets containing approximately 180 mg. of gastric/intestinal fluid in a Bath #6 equipped with a 50 r.p.m. paddle stirrer.

EXAMPLE 2

A single-dose clinical study was undertaken to evaluate the pharmacokinetics of the preferred timed-release verapamil/trandolapril combination according to the invention. The Angiotensin Converting Enzyme (ACE) activity was also evaluated.

This was an open-label, single-dose pilot study of 36 hours duration. The single dose contained trandolapril (2 mg.) and verapamil (ISOPTIN SR) (180 mg.) in a single tablet. (The 2 mg. of trandolapril was incorporated into the slow release alginate matrix of the slow release verapamil tablet).

A total of six healthy white adult males were enrolled in

the study. Subjects had a mean age of 30.3 years and a mean weight f 157.5 lbs.

Th study drug was administered sequentially to subjects at five minute intervals beginning at 8:30 a.m. All subjects received a single dose of the study drug immediately following a standardized breakfast.

No significant adverse reactions were reported during the study. No clinically significant abnormal vital signs, ECG or clinical laboratory findings were reported during the study.

Mean pharmacokinetic parameters for trandolapril, trandolaprilat (the active metabolite of trandolapril), verapamil and norverapamil (the active metabolite of verapamil) were as follows:

	C_{max}	T_{max} (hours)	AUC_{0-36}
Trandolapril	296.8 pg/mL	5.2	1483.8 pg/mL/hr
Trandolaprilat	1239 pg/mL	22	32442.3 pg/mL/hr
Verapamil	44.8 ng/mL	8.3	473.5 ng/mL/hr
Norverapamil	51.0 ng/mL	11.3	867.1 ng/mL/hr

A graph of the average verapamil and norverapamil concentrations over time and shown in Figure 1. Verapamil and norverapamil concentrations begin to peak at about 8 hours. A graph of the average trandolapril and trandolaprilat concentrations over time are shown in Figure 2. Concentrations of trandolapril peak at approximately 5 hours after dosing, while the level of trandolaprilat begins to peak at about 10 hours and stays at approximately that level for the duration of the study.

The Angiotensin Converting Enzyme or ACE Activity was also evaluated during the study. Mean (±SD) ACE activity was as

follows:

ACE Activity (Activity Units)

Baseline	Hours Post-Dosing								
0 Hour	0.5	1.0	2.0	3.0	4.0	6.0	8.0	24	36
5.2 (1.05)	5.2 (1.14)	4.8 (0.96)	4.8 (1.45)	3.6 (1.57)	2.6 (0.93)	1.8 (1.31)	1.8 (0.72)	0.8 (0.49)	1.1 (0.60)

Normal Range = 2.0-7.5 Activity Units

ACE Activity (% of Baseline)

Baseline	Hours Post Dosing								
0 Hour	0.5	1.0	2.0	3.0	4.0	6.0	8.0	24	36
100	100	92.3	92.3	69.2	50	34.6	34.6	15.4	21.2

The results indicate that ACE activity begins to fall below the normal range at somewhere between about 4 to 6 hours after dosing.

Next, a comparison in ACE activity levels was made between the extended-release formulation of verapamil and trandolapril according to the preferred embodiment of the invention, and an immediate release formulation of trandolapril alone. The results are indicated in the chart of Figure 3. TV-1 represents the ACE activity as a % of baseline activity versus time for the immediate release formulation of trandolapril, while TV-2 represents the ACE activity versus time for the extended release formulation of 180 mg. of verapamil with 2 mg. of trandolapril.

The comparison of ACE activity for TV-2 vs. TV-1 was such that after approximately 24 hours, there were relatively insignificant differences in ACE inhibition between the timed-release composition of verapamil and trandolapril according to the preferred embodiment of the invention when compared with the standard immediate-release formulation.

Also provided as part of the invention is an improved method of treating hypertension of high blood pressure, and related coronary problems which comprises administering to a patient a therapeutically effective quantity of a timed-release formulation of both one or more calcium channel blockers and one or more ACE

inhibitors in combination with a pharmaceutically acceptable carrier or vehicle. It is highly desirable that the timed-release formulation will comprise verapamil HCl and trandolapril according to the preferred embodiment of the invention, and will be administered to a patient orally once daily. Thus, improved method of treating hypertension etc. will comprise administering to a patient a timed-release formulation comprising about 180 mg. of verapamil and 2 mg. of trandolapril in combination with a pharmaceutically effective carrier.

Other treatment regimens consistent with the overall goal of maintaining low ACE activity levels for the duration of treatment are also within the scope of the invention.

While the invention has been described in detail in its various embodiments for the purpose of illustration, it is to be understood that such description is solely for that purpose and that variations may be made therein by those skilled in the art without department from the spirit and scope of the invention as set forth in the following claims.

CLAIMS

What is claimed is:

1. A pharmaceutical composition for the treatment of hypertension, congestive heart failure and other coronary ailments in mammals which comprises a therapeutically effective quantity of both one ore more calcium channel blocking agents and one ore more ACE inhibitors in time-released form in combination with a pharmaceutically acceptable carrier.

2. A pharmaceutical composition as claimed in Claim 1, wherein said calcium channel blocking agents are selected from the group consisting of diltiazem, nicardipine, nifedipine, nimodipene, verapamil and mixtures thereof, and said ACE inhibitors are selected from the group consisting of captopril, enalapril, lisinopril, trandolapril and mixtures thereof.

3. A pharmaceutical composition as claimed in Claim 2, wherein said calcium channel blocking agent is verapamil and said ACE inhibitor is trandolapril.

4. A pharmaceutical composition as claimed in Claim 3, wherein the weight ratio of verapamil to trandolapril in said composition is about 90:1/

5. A pharmaceutical composition as claimed in Claim 4, wherein said verapamil and said trandolapril are present in a slow release core tablet c mprising a core matrix f verapamil and trandolapril.

6. A pharmaceutical composition for the treatment of hypertension, congestive heart failure and other coronary ailments, comprising a therapeutically effective quantity of both verapamil and trandolapril in time-released form in combination with a pharmaceutically acceptable carrier.

7. A pharmaceutical composition as claimed in Claim 6, wherein the weight ratio of verapamil to trandolapril in said composition is 90:1.

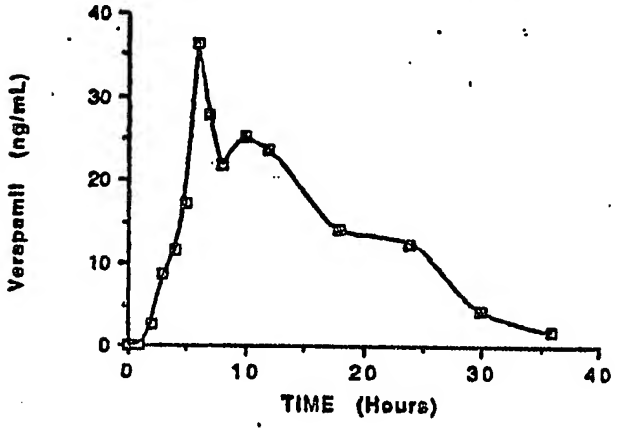
8. A pharmaceutical composition as claimed in Claim 7, wherein said compositions administered orally once daily.

9. An improved method for the treatment of hypertension and related coronary problems in mammals which comprises administering to a patient a therapeutically effective quantity of a time-released formulation of one or more calcium channel blockers and one or more ACE inhibitors in combination with a pharmaceutically acceptable vehicle.

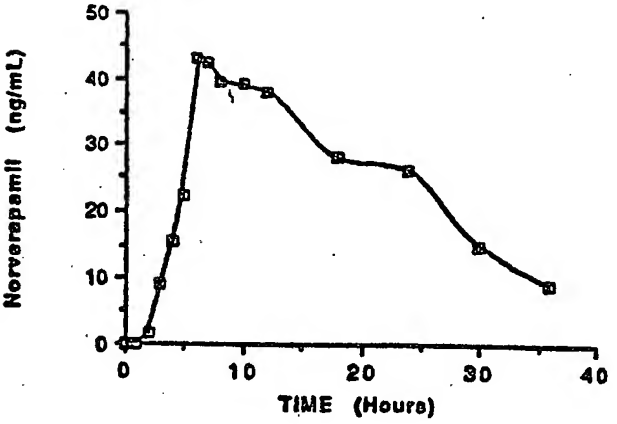
10. An improved method as claimed in Claim 9, wherein said composition is administered to a patient orally once daily.

FIG. 1

AVERAGE VERAPAMIL CONCENTRATIONS



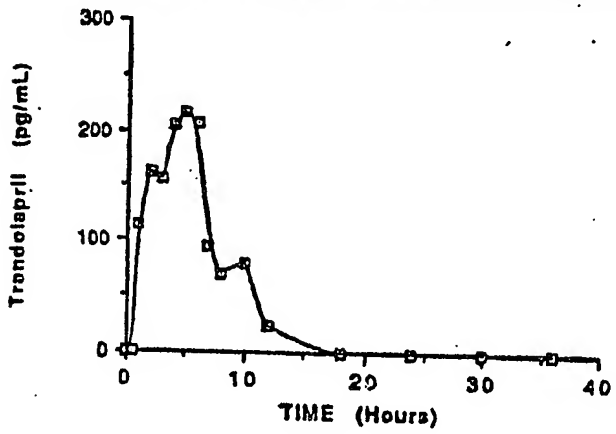
AVERAGE NORVERAPAMIL CONCENTRATIONS



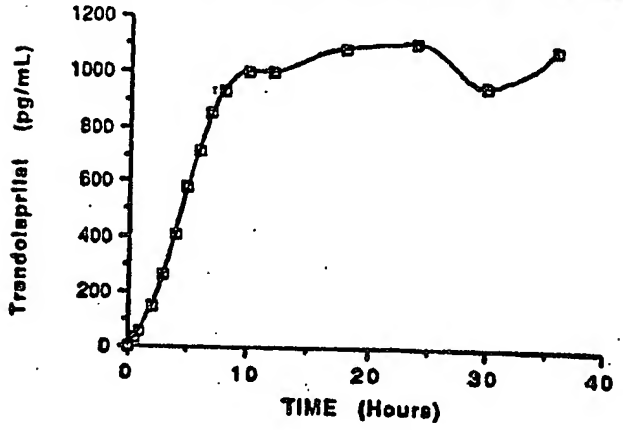
Patent Agents

FIG. 2

AVERAGE TRANDOLAPRIL CONCENTRATIONS

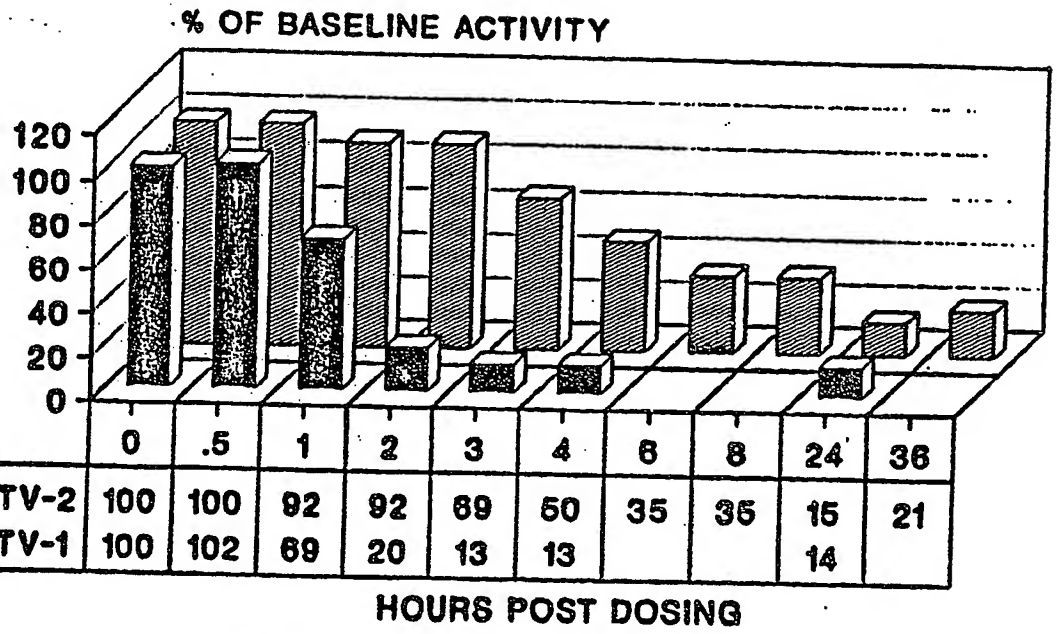


AVERAGE TRANDOLAPRILAT CONCENTRATIONS



Patent Agents

ACE ACTIVITY COMPARISONS
ACE ACTIVITY (%)



	0	.5	1	2	3	4	6	8	24	36
STUDY TV-2	100	100	92	92	69	50	35	35	15	21
STUDY TV-1	100	102	69	20	13	13			14	

STUDY TV-2 EVALUATED ACE ACTIVITY WITH TRANDOLAPRIL ADDED TO THE ISOPTIN-SR FORMULATION.

Patent Agents

FIG. 3

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